REMARKS

Discussion of Specification and Claim Amendments

The specification has been amended to include a reference to perflubron (as recited in original claim 3). Claim 16 has been amended to correct a minor grammatical error. Duplicate entries of "sodium carboxymethyl cellulose" and "a sorbitan fatty acid ester" have been removed from claims 18 and 32. Claims 17-18, 23-25, 31-32, and 36-37 have been amended to expedite the prosecution of this application. No new matter has been added.

The Office Action

The Office Action sets forth the following grounds for rejection: (1) claims 16-18, 20-32, and 34-38 are rejected under 35 U.S.C. § 102(a), as allegedly anticipated by WO 99/29300 (RTP Pharma); (2) claims 16-18, 20-32, and 34-38 are rejected under 35 U.S.C. § 102(a), as allegedly anticipated by WO 99/29316 (Severson et al.); (3) claims 16-38 are rejected under 35 U.S.C. § 102(b), as allegedly anticipated by U.S. Patent No. 5,656,289 (Cho et al.); (4) claims 16-27 and 30-38 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over U.S. Patent No. 5,660,858 (Parikh et al.) in view of U.S. Patent No. 5,091,187 (Haynes); and (5) claims 16-38 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

The Present Invention

The present invention is directed to surface modified particulate compositions of biologically active substances and processes for preparing a dosage form of a biologically active substance. Claims 16-38 are currently pending. A set of pending claims is attached.

Discussion of Anticipation Rejections

Claims 16-18, 20-32, and 34-38 are rejected under 35 U.S.C. § 102(a), as allegedly anticipated by RTP Pharma and by Severson et al. The Office Action contends that RTP Pharma teaches a self-emulsifying composition containing a hydrophobic drug, a hydrophobic liquid, a surfactant, and a hydrophilic component, with particle sizes from 10 nm to 10 microns and that Severson et al. teaches a self-emulsifying composition containing a hydrophobic drug (cyclosporin), a hydrophobic liquid, a surfactant, and a hydrophilic component, with particle sizes from 10 nm to 10 microns. Applicants respectfully traverse these rejections.

A reference anticipates a claimed invention only if it discloses each and every element of the claimed invention. RTP Pharma and Severson et al. fail to disclose a non-aqueous

hydrophobic liquid in which said biologically active substance is not soluble or is poorly soluble as required by the present claims. Indeed, RTP Pharma teaches a composition comprising fenofibrate as the active ingredient solubilized in a carrier medium comprising at least one hydrophobic component, at least one hydrophilic component, and at least one surfactant (page 1, third full paragraph and page 4, last paragraph). Severson et al. discloses pharmaceutical compositions containing an omega-3 fatty acid and a therapeutic agent that is substantially soluble in the omega-3 fatty acid. For this reason alone, the anticipation rejections over RTP Pharma and Severson et al. are improper and should be withdrawn.

Additionally, neither RTP Pharma nor Severson et al. discloses solid particles of a water-insoluble biologically active substance of a volume weighted mean particle size in the range of 0.01 to 10 micrometers as required in the present claims, since the cited references disclose dissolving the active ingredient, rather than suspending solid particles. The "particle sizes" provided by the cited references are the sizes of the liquid droplets formed upon dispersion in the aqueous medium and not the size of the solid particle of the biologically active substance as in the present claims. Thus, the compositions of RTP Pharma and Severson et al. including the dissolved active ingredient in a hydrophobic liquid are distinctly different from the presently claimed invention.

Claims 16-38 are rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Cho et al. The Office Action contends that Cho et al. teaches a pharmaceutical composition containing insulin, oleic acid, ethanol, and lecithin in Example 1 and that the particle size is 1.5-2 mm in Examples 13 and 16. Applicants respectfully traverse this rejection.

Cho et al. fails to disclose a composition comprising, inter alia, particles of a water-insoluble biologically active substance of a volume weighted mean particle size in the range of 0.01 to 10 micrometers, and for this reason alone, the rejection is improper. As the Office Action correctly notes, Cho et al. discloses in Example 16 a particle size of 1.5 to 2 millimeters. Contrary to the assertion in the Office Action, Example 13 of Cho et al. fails to disclose any particle size. Examples 3, 8, 10, 11 and 12, referred to in Example 13, also fail to disclose a particle size. In Example 1, Cho et al. discloses a droplet size of the micro-emulsion. This droplet contains a liquid and not solid particles. Note the insulin is dissolved (col. 16, lines 55-65). Additionally, Cho et al. fails to disclose a composition including a quantity of not more than about 10% of the total weight of the composition of one or more hydrophilic substances.

In view of all of the foregoing, the anticipation rejections should be withdrawn.

Discussion of Obviousness Rejection

Claims 16-27 and 30-38 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Parikh et al. in view of Haynes. The Office Action contends that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Parikh et al. and Haynes to arrive at the claimed invention. Applicants respectfully traverse this rejection.

The Office Action has failed to make a *prima facie* case for obviousness. There is no motivation to combine Parikh et al. and Haynes. Parikh et al. teaches away from the presently claimed invention. Parikh et al. is directed to pharmaceutical compositions containing a cyclosporin dissolved in a synthetic medium chain triglyceride, and is particularly directed to the use of medium chain length triglycerides and free fatty acids to enhance the solubility of the cyclosporin in the oil phase (col. 1, lines 3-7). Furthermore, Parikh et al. teaches that the oil containing the dissolved cyclosporin, is added to an aqueous solution and homogenized to form an emulsion.

The presently claimed invention, in contrast to Parikh et al., relates to a composition comprising solid particles of a biologically active substance dispersed in a non-aqueous carrier system comprised of a hydrophobic liquid in which said biologically active substance is not soluble or is poorly soluble, wherein the composition self-disperses upon addition to a fluid aqueous medium. A hydrophobic liquid in which the biologically active substance is not soluble or is poorly soluble is a requirement in the presently claimed invention. In contradistinction, the biologically active substance must be soluble in the hydrophobic liquid in Parikh et al. Furthermore, the composition of the present invention self-disperses upon addition to a fluid aqueous medium. Parikh et al. does not disclose such a composition.

Haynes also teaches away from the presently claimed invention. Haynes is directed to phospholipid-coated microcrystals of water-insoluble drugs suspended in an aqueous solution. The presently claimed invention, in contrast to Haynes, is directed to a composition including, inter alia, one or more hydrophilic substances that provide a self-dispersing property to the composition when the composition is added to an aqueous medium. In contradistinction, Haynes does not disclose or fairly suggest a composition including one or more hydrophilic substances that self-disperses upon addition to an aqueous medium. Haynes discloses a suspension of solid particles in an aqueous medium. Motivation to combine Parikh et al. and Haynes, if any, can come only from a hindsight reconstruction employing applicants' invention as a road map. Hindsight reconstruction is impermissible under the law. Haynes fails to suggest a composition having a spontaneous dispersing property. The composition of the present invention does not require significant energy input for dispersion.

One of skill in the art would simply never be led from the teachings of Parikh et al. and Haynes to arrive at the presently claimed invention.

Even if a combination is made, the combination does not suggest to those of ordinary skill in the art the presently claimed invention. For example, the combination does not suggest a composition having spontaneous dispersing property.

Further, the composition of the claimed invention has an unexpected and superior property, i.e., the self-dispersing property of the presently claimed invention that gives a particle size stability not realized in the suspension arguably suggested by the combination of the cited references.

In view of the foregoing, the obviousness rejection of claims 16-38 should be withdrawn.

Discussion of the Indefiniteness Rejection

The Office Action contends that the intended meaning of the recitation in claims 16 and 30 of "non-aqueous hydrophobic liquid" is unclear. The Office Action also contends that the distinction between "hydrophobic liquid" and "surfactants" in claim 16 is unclear. The Office Action further contends that it is unclear how the celluloses recited in claims 18 and 32 are considered as surfactants.

The amendment to claims 17 and 31 deleting "glycerin" and "a pharmaceutically acceptable polyhydroxy compound" render the meaning of "non-aqueous hydrophobic liquid" in claims 16 and 30 more clear.

Further, applicants respectfully point out that claims 17 and 31 recite "monohydric alcohols" and "polyhydric alcohols" as hydrophobic components, while claims 20 and 34 recite "low-molecular weight monohydric alcohols" and "low-molecular weight polyhydric alcohols" as hydrophilic components. Applicants respectfully traverse the rejection. One of skill in the art would know that the scope of these terms are different. For example, mono-, di- or polyhydric alcohols of sufficient chain length would be hydrophobic. Those of ordinary skill in the art would know that low molecular weight mono-, di- or polyhydric alcohols can be hydrophilic.

The amendment to claims 18 and 32 deleting "triacetin", "a substituted cellulose derivative", "methylcellulose", "hydroxycellulose", "hydroxy propylcellulose", "hydroxy propylmethylcellulose", and "noncrystalline cellulose" render the distinction between "hydrophobic liquid" and "surfactant" in claim 16 more clear. One of ordinary skill in the art would know that monoglycerides, diacetin, and monoacetin have hydrophobic and hydrophilic moieties and can act as surfactants. One of skill in the art would also know that

the celluloses recited in present claims 18 and 32 are surfactants. Accordingly, Applicants submit that the claims are not indefinite and the rejection should be withdrawn.

The Office Action contends that it is unclear what applicants intend to convey by "fish oil free fatty acid" and questions whether the fatty acids are prepared from fish oil. Applicants respectfully traverse this rejection. The Office Action's interpretation is correct and Applicants respectfully submit that one of ordinary skill in the art would know that "fish oil free fatty acid" defines fatty acids prepared from fish oil.

The Office Action further questions the distinction between alkanol, monohydric alcohol, and dihydric alcohol. Applicants respectfully traverse this rejection and submit that one of ordinary skill in the art would know the distinction. Alkanol is a saturated alcohol, while monohydric alcohol and dihydric alcohol may be a saturated alcohol or unsaturated alcohol. A monohydric alcohol includes a single hydroxyl group and a dihydric alcohol includes two hydroxyl groups.

The Office Action also asks what is "perflubron". Applicants respectfully traverse this rejection and submit that one of ordinary skill in the art would know what perflubron is. Perflubron is known to those skilled in the art as a synthetic second generation brominated fluorocarbon (1-bromo-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane). A copy of page 7234 from *The Merck Index*, Thirteenth Edition (2001), identifying perflubron is attached. The Office Action asks what is "a protein used in the treatment of diabetes" in claims 22 and 35 and asks whether applicants mean insulin. Applicants respectfully traverse this rejection and submit that one of skill in the art would know that a number of proteins can be used in the treatment of diabetes, including, but not limited to insulin. For example, gastrin has been proposed. (See attached copy of U.S. Patent No. 5,885,956 to Nardi et al., col. 2, lines 9-11). Since "derivatives of insulin" has been deleted from claims 23 and 36, the rejection based on this phrase is moot.

The Office Action contends that the distinction between "water containing soluble agents for lyoprotection" and "water containing pharmaceutically acceptable lyoprotectants" and expressions used for cryoprotectants and polyols is unclear. The amendment to claims 25 and 37 renders this rejection moot.

The Office Action rejects claims 26 and 38, contending that the claims recite several body fluids and is unclear. Applicants respectfully traverse this rejection. As an initial point, Applicants respectfully point out that parent claims 16 and 31 (upon which claims 26 and 38 are dependent) recite, "upon addition of said composition to a fluid aqueous medium". The claims do not recite that "the fluid is added to the composition", as the Office Action states. The claims must be interpreted based on the claim language. Applicants submit that the purpose of collecting body fluid and adding the composition so that the composition self-

disperses is clear to one of ordinary skill in the art. As explained in the specification, for example, at page 11, lines 13-15, fluids from an individual patient are inherently biocompatible in most cases with that individual, and a suspension prepared from a composition of this invention in a fluid from a patient, such as blood, can be administered to that patient as a biocompatible fluid suspension. Accordingly, the rejection of claims 26 and 38 should be withdrawn.

The Office Action contends that a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation is considered indefinite, referring to the explanation given by the Board of Patent Appeals and Interferences in *Ex Parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), where broad language was followed by "such as" and then narrow language. Applicants respectfully traverse the rejection of claims 17-18, 20, 25, 27, 31-32, and 34.

The present claims do not include broad language followed by "such as" and then narrow language, indeed, the present claims do not include "such as" at all. Any overlap of claimed subject matter between various terms does not contravene the statute. One of ordinary skill in the art reading the claims would be able to ascertain with a reasonable degree of precision and particularity, the particular area set out and circumscribed by the claims. Fish oil is an embodiment of an oil derived from an animal origin. The terms "cellulose derivatives", "methylcellulose", "hydroxycellulose" "hydroxy propylcellulose", and "hydroxy propylmethylcellulose" have been deleted.

The amendment to claim 24 renders the rejection relating to the term "for use" moot.

In view of the foregoing, the indefinite rejections of claims 16-38 should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance. Should there remain any issues outstanding, the Examiner is invited to call the undersigned at her Washington, D.C. office.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PACE et al.

Application No. 09/667,328

Filed: September 21, 2000

Art Unit: 1616

Examiner: S. S. Gollamudi

For: SURFACE MODIFIED PARTICULATE COMPOSITIONS OF BIOLOGICALLY ACTIVE SUBSTANCES

AMENDMENTS TO SPECIFICATION AND CLAIMS MADE IN RESPONSE TO THE OFFICE ACTION DATED JANUARY 7, 2002

Amendments to the paragraph beginning at page 11, line 23:

Preferred non-aqueous media of the carrier system include hydrophobic components such as triglycerides, diglycerides, monoglycerides, free fatty acids, and fatty acid esters and derivatives thereof, individually or in combination. Examples of such hydrophobic components include but are not limited to propylene glycol dicaprylate/caprate, caprilic/capric triglyceride, caprylic/capric/linoleic triglyceride, e.g. synthetic medium chain triglycerides having C_{8-12} fatty acid chains or other derivatized (synthetic) triglycerides of the type known and commercially available under Miglyol 810, 812, 818, 829 and 840, linoleic acid, linoleic acid ethyl ester, fish oils as free fatty acids, their esterification and their transesterification products, e.g. of the type known and commercially available under EPAX6000FA, EPAX4510TG, individually or in combination. Additional examples include vegetable oils and C_{12-18} fatty acid mono-, di- and triglycerides prepared by individual admixing or as transesterification products of vegetable oils (such as soybean oil, almond oil, sunflower oil, olive oil or corn oil) with glycerol and perfluhron.

Amendments to existing claims:

16. (Amended) A composition comprising stable solid particles of a water-insoluble biologically active substance of a volume weighted mean particle size in the range of 0.01 to 10 micrometers, which particles are dispersed in a non-aqueous carrier system comprised of:

a non-aqueous hydrophobic liquid in which said biologically active substance is not soluble or is poorly soluble;

a surfactant system consisting of at least one surfactant which is soluble in said non-aqueous hydrophobic liquid, wherein at least a portion of which surfactant system absorbs to the surface of said particles; and

a quantity of not more than about 10% of the total weight of said composition of one or more hydrophilic substances that provides a self-dispersing property to said composition,

wherein upon addition of said composition to a fluid aqueous medium, said composition self-disperses in said fluid aqueous medium to form a suspension comprising droplets of non aqueous hydrophobic liquid containing particles of surface stabilized water-insoluble biological substance suspended in the oily droplets of the dispersion and particles of said water-insoluble biologically active substance migrated into said fluid aqueous medium wherein said particles have a size in the range of 0.01 to 10 micrometers and have associated therewith on the surface at least a portion of said surfactant system.

17. (Amended) The composition of claim 16 where at least one component of the non-aqueous hydrophobic liquid is selected from the group consisting of an oil derived from animal origin; a vegetable oil; a fish oil; a fish oil free fatty acid; oleic acid; linoleic acid; a poly-unsaturated fatty acid; caprilic/capric triglyceride; caprylic/capric/linoleic triglyceride; a synthetic medium chain triglyceride having a C_{8-12} fatty acid chain; propylene glycol dicaprylate/caprate; linoleic acid ethyl ester; a cholesteryl fatty acid ester, a C_{12-18} fatty acid monoglyceride, a C_{12-18} fatty acid diglyceride, and a C_{12-18} fatty acid triglyceride prepared from soybean oil, almond oil, sunflower oil, olive oil, and corn oil with glycerol; a pharmaceutically acceptable monohydric alcohol; a pharmaceutically acceptable alkanol; a pharmaceutically acceptable dihydric alcohol; ~~a pharmaceutically acceptable polyhydroxy compound; glycerin;~~ a pharmaceutically acceptable aromatic ester; benzyl benzoate; diethyl phthalate; propyl gallate; triacetin; diacetin; monoacetin; triethyl citrate; a pharmaceutically suitable hydrophobic organic solvent; a hydrofluorocarbon in the liquid state at ambient temperature and pressure; and perflubron.

18. (Amended) The composition of claim 16 where at least one surfactant component is selected from the group consisting of a natural or synthetic amphiphilic agent; a phospholipid; a nonionic surfactant; a polyoxyethylene fatty alcohol ether; a sorbitan fatty acid ester; a polyoxyethylene sorbitan fatty acid ester; glycerol triacetate; ~~triacetin;~~ a polyethylene glycol; cetyl alcohol; cetostearyl alcohol; stearyl alcohol; a poloxamer; a polaxamine; a

polyoxethylene castor oil derivative; vitamin E; D-alpha-tocopheryl polyethylene glycol 1000 succinate; vitamin E TPGS; a PEG glyceryl fatty acid ester; PEG-8 glyceryl caprylate/caprate; PEG-4 glyceryl caprylate/caprate; PEG-32 glyceryl laurate; PEG-6 glyceryl mono oleate; PEG-6 glyceryl linoleate; a propylene glycol mono fatty acid ester; a propylene glycol di-fatty acid ester; propylene glycol laurate; propylene glycol caprylate/caprate; diethylene glycol monoethyl ether; transcutol; ~~a sorbitan fatty acid ester;~~ a monoglyceride; an acetylated monoglyceride; glycerol monooleate; glycerol monostearate; a mono-acetylated monoglyceride; a di-acetylated monoglyceride; monoacetin; diacetin; an anionic surfactant; a fatty acid salt; a bile salt; potassium laurate; triethanolamine stearate; sodium lauryl sulfate; an alkyl polyoxyethylene sulfate; sodium alginate; dioctyl sodium sulfosuccinate; sodium carboxymethylcellulose; calcium carboxymethylcellulose; a cationic surfactant; a pharmaceutically acceptable quaternary ammonium compound; benzalkonium chloride; cetyltrimethylammonium bromide; lauryldimethylbenzylammonium chloride; ~~a substituted cellulose derivative; methylcellulose; hydroxycellulose; hydroxy propylcellulose; hydroxy propylmethylcellulose; nonerystalline cellulose; sodium carboxymethyl cellulose;~~ polyethylene glycol; PEG 1000; PEG 1500; and PEG 3400.

23. (Amended) The composition of claim 16, wherein the biologically active substance is selected from the group consisting of nifedipine, ursodiol, budesonide, peclitaxel, camptothecin, a derivative of peclitaxel, a derivative of camptothecin, piroxicam, itraconazole, acyclovir, a derivative of acyclovir, fenofibrate, cyclosporine, and insulin~~; and a derivative of insulin~~.

24. (Amended) The composition of claim 16 ~~for use in~~ which is prepared for sustained or controlled delivery of the biologically active substance.

25. (Amended) The composition of claim 16 where the fluid aqueous medium is selected from the group consisting of water, buffered water, phosphate buffered water, phosphate buffered saline, citrate buffered water, acetate buffered water, water buffered with pharmaceutically acceptable pH controlling agents, water containing salts, water containing sodium chloride, water containing pharmaceutically acceptable salts, water containing soluble agents for lyoprotection, water containing soluble agents for cryoprotection, water containing dextrose, water containing mannitol, water containing trehalose, water containing sucrose, water containing sorbitol, ~~water containing pharmaceutically acceptable lyoprotectants; water containing pharmaceutically acceptable cryoprotectants;~~ water containing polyhydroxy-

containing compounds, ~~water containing sugars, water containing polyols,~~ and a mixture thereof.

31. (Amended) The process of claim 30 where at least one component of the non-aqueous hydrophobic liquid is selected from the group consisting of an oil derived from animal origin; a vegetable oil; a fish oil; a fish oil free fatty acid; oleic acid; linoleic acid; a poly-unsaturated fatty acid; caprilic/capric triglyceride; caprylic/capric/linoleic triglyceride; a synthetic medium chain triglyceride having a C_{8-12} fatty acid chain; propylene glycol dicaprylate/caprate; linoleic acid ethyl ester; a cholesteryl fatty acid ester, a C_{12-18} fatty acid monoglyceride, a C_{12-18} fatty acid diglyceride, and a C_{12-18} fatty acid triglyceride prepared from soybean oil, almond oil, sunflower oil, olive oil, and corn oil with glycerol; a pharmaceutically acceptable monohydric alcohol; a pharmaceutically acceptable alkanol; a pharmaceutically acceptable dihydric alcohol; ~~a pharmaceutically acceptable polyhydroxy compound; glycerin;~~ a pharmaceutically acceptable aromatic ester; benzyl benzoate; diethyl phthalate; propyl gallate; triacetin; diacetin; monoacetin; triethyl citrate; a pharmaceutically suitable hydrophobic organic solvent; and a hydrofluorocarbon in the liquid state at ambient temperature and pressure.

32. (Amended) The process of claim 30 where at least one surfactant component is selected from the group consisting of a natural or synthetic amphiphilic agent; a phospholipid; a nonionic surfactant; a polyoxyethylene fatty alcohol ether; a sorbitan fatty acid ester; a polyoxyethylene sorbitan fatty acid ester; glycerol triacetate; ~~triacetin;~~ a polyethylene glycol; cetyl alcohol; cetostearyl alcohol; stearyl alcohol; a poloxamer; a polaxamine; a polyoxethylene castor oil derivative; vitamin E; D-alpha-tocopheryl polyethylene glycol 1000 succinate; vitamin E TPGS; a PEG glyceryl fatty acid ester; PEG-8 glyceryl caprylate/caprate; PEG-4 glyceryl caprylate/caprate; PEG-32 glyceryl laurate; PEG-6 glyceryl mono oleate; PEG-6 glyceryl linoleate; a propylene glycol mono fatty acid ester; a propylene glycol di-fatty acid ester; propylene glycol laurate; propylene glycol caprylate/caprate; diethylene glycol monoethyl ether; transcutol; ~~a sorbitan fatty acid ester;~~ a monoglyceride; an acetylated monoglyceride; glycerol monooleate; glycerol monostearate; a mono-acetylated monoglyceride; a di-acetylated monoglyceride; monoacetin; diacetin; an anionic surfactant; a fatty acid salt; a bile salt; potassium laurate; triethanolamine stearate; sodium lauryl sulfate; an alkyl polyoxyethylene sulfate; sodium alginate; dioctyl sodium sulfosuccinate; sodium carboxymethylcellulose; calcium carboxymethylcellulose; a cationic surfactant; a pharmaceutically acceptable quaternary ammonium compound; benzalkonium chloride; cetyltrimethylammonium bromide; lauryldimethylbenzylammonium chloride; ~~a substituted~~

~~cellulose derivative; methylcellulose; hydroxycellulose; hydroxy propylcellulose; hydroxy propylmethylcellulose; noncrystalline cellulose; sodium carboxymethyl cellulose;~~ polyethylene glycol; PEG 1000; PEG 1500; and PEG 3400.

36. (Amended) The process of claim 30, wherein the biologically active substance is selected from the group consisting of nifedipine, ursodiol, budesonide, peclitaxel, a derivative of peclitaxel, camptothecin, a derivative of camptothecin, piroxicam, itraconazole, acyclovir, a derivative of acyclovir, cyclosporine, and insulin~~; and a derivative of insulin~~.

37. (Amended) The process of claim 30, wherein the fluid aqueous medium is selected from the group consisting of water, buffered water, phosphate buffered water, phosphate buffered saline, citrate buffered water, acetate buffered water, water buffered with pharmaceutically acceptable pH controlling agents, water containing salts, water containing sodium chloride, water containing pharmaceutically acceptable salts, water containing soluble agents for lyoprotection, water containing soluble agents for cryoprotection, water containing dextrose, water containing mannitol, water containing trehalose, water containing sucrose, water containing sorbitol, ~~water containing pharmaceutically acceptable lyoprotectants, water containing pharmaceutically acceptable cryoprotectants;~~ water containing polyhydroxy-containing compounds, ~~water containing sugars; water containing polyols;~~ and a mixture thereof.